Clinical Pharmacology Update

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Newer agents in the treatment of arterial hypertension[1]

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Many new effective pharmacologic agents have been developed and marketed over the last decade for the treatment of hypertension. A number of beta blocking agents are now available for use in combination with thiazide diuretics or as monotherapy in selected hypertensive patients. All of the beta blockers are effective antianginal agents and appear to decrease the rate of sudden death and myocardial infarction in the postinfarction period. Calcium channel blocking agents share the antianginal effects of the beta blockers and also appear to be useful antihypertensive agents, although they are not approved for the latter use at this time. Converting enzyme inhibitors have been utilized with increasing frequency, both in patients with renovascular and essential hypertension. These agents have become increasingly popular because of their relative freedom from many of the side effects associated with other classes of antihypertensive drugs. Several new central and peripherally acting sympatholytic agents have also been marketed, but they do not appear to differ significantly from the older agents of this class. These new drugs provide considerable versatility for the clinician who treats hypertensive patients, but they have not replaced the older drugs which have proved to be effective in the treatment of hypertension.

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Epidemiologic evidence leaves little doubt that even mild increments in either systolic or diastolic blood pressure are associated with an increased incidence of premature mortality from cardiovascular disease.[1,2] Findings from the Hypertension Detection and Follow-up Program Cooperative Group suggest that there are at least 35 million hypertensive patients, the majority (70%) of whom have blood pressures which are only minimally increased. Results of this study suggest that a systematic, stepped-care approach to the treatment of hypertension utilizing diuretic agents, adrenergic inhibiting drugs, and vasodilators in a sequential fashion effectively reduces blood pressure in most patients. This reduction has been associated with a decreased incidence of stroke and myocardial infarction over a five-year period.[3]

The pharmaceutical industry has responded by developing a number of agents with varying pharmacologic properties for the treatment of hypertension (*Table*). A thorough knowledge of the clinical pharmacology of these agents allows the choice of an effective, well-tolerated treatment program for the vast majority of hypertensive patients. This report will acquaint the clinician with the clinical pharmacology and use of these new agents.

Beta blockers

Over the last decade, beta blocking agents have been used alone or in combination with thiazide diuretics with increasing frequency because of

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Table Newer antihypertensive agents

A.	Beta blockers
	1. Atenolol
	2. Timolol
	3. Pindolol
	4. Labetalol
B.	Other adrenergic inhibitors
	1. Guanabenz
	2. Guanadrel
C.	Converting enzyme inhibitors
	1. Captopril
	2. Enalapril maleate
D.	Calcium channel blockers
	1. Nifedipine
	2. Verapamil
	3. Diltiazem

their efficacy, relative freedom from metabolic and symptomatic side effects, and utility in the treatment of a variety of associated medical conditions such as angina pectoris, migraine headache, essential tremor, and atrial tachyarrhythmias. Although their efficacy is similar, these different beta blocking agents possess certain pharmacologic properties which may be clinically applicable in the management of individual hypertensive patients.

Atenolol (Tenormin)

Atenolol was the first cardioselective beta blocking agent approved for once daily administration in the treatment of hypertension. Approximately 50% of an orally administered dose is absorbed. It does not undergo extensive first-pass metabolism in the liver and is not extensively protein-bound. Most of the drug is excreted unchanged by the kidney, which accounts for its relatively long duration of action and the lack of interindividual variability in dosage requirements. Thus, it is a convenient agent to use since few patients achieve an added antihypertensive effect when the dose is increased above 100 mg/day.[4] In contrast, beta blocking agents such as propranolol, which undergo extensive first-pass hepatic metabolism, must be titrated for each individual, since the degree of hepatic metabolism and protein-binding varies from patient to patient.[5]

Atenolol is not lipid-soluble and does not cross the blood/brain barrier. This may account for the relative absence of central nervous system side effects. Like propranolol, atenolol should be avoided in patients with bronchial asthma, congestive heart failure, severe sinus bradycardia, or heart block greater than first degree. It does not possess intrinsic sympathomimetic activity (ISA) or membrane-stabilizing properties.

Atenolol is given as a single oral dose of 50–100 mg/day. The drug may accumulate in patients with chronic renal failure if the glomerular filtration rate is less than approximately 35 ml/min/1.73 m^2. It is available in 50- and 100-mg tablets.

Timolol maleate (Blocadren)

Timolol is rapidly and nearly completely absorbed from the gastrointestinal tract. It is not extensively protein-bound but undergoes approximately 50% first-pass hepatic metabolism. The unmetabolized drug is excreted by the kidneys.

Timolol was the first beta blocking agent shown to reduce the frequency of reinfarction and sudden death after myocardial infarction.[6] This property appears to be shared by the beta blocking drugs as a class.[7] The side effects of timolol are similar to those of propranolol. Timolol is available in 10- and 20-mg tablets, and dosages range from 20 to 60 mg/day. It is usually given twice daily, and its antihypertensive effects are comparable to those of the other beta blockers when administered in equipotent doses.

Pindolol (Visken)

Pindolol is well absorbed, 40%–60% protein-bound, and excreted by both the liver and kidneys. Its pharmacologic half life of 3–4 hours is prolonged in patients with renal failure. It is a noncardioselective beta adrenergic receptor blocker that possesses intrinsic sympathomimetic activity. Thus it has the ability to stimulate beta receptors at low levels of sympathetic tone. Because of this property, pindolol does not reduce resting heart rate to the same degree as the beta blockers that do not possess ISA. However, pindolol blocks the heart rate response to exercise as effectively as other beta adrenergic receptor blocking agents and is an effective antianginal agent.[8]

The toxicologic profile of pindolol is similar to that of the other beta blockers, but Raynaud's phenomenon, cold extremities, or resting bradycardia may occur less frequently than they do with beta blockers that lack ISA. It should not be

used in patients with bronchial asthma, congestive heart failure, or heart block greater than first degree.

Pindolol is available in 5- and 10-mg tablets, and the dosage range is generally between 15 and 60 mg/day. It may be given twice daily alone or in combination with a thiazide diuretic.

Labetalol (Normodyne)

This is actually a combined alpha and beta adrenergic receptor blocking agent. As with prazosin, alpha blockade with labetalol is selective for post-synaptic alpha$_1$ receptors. The beta blockade is noncardioselective, but the agent appears to have selective intrinsic sympathomimetic activity for beta$_2$ receptors in the periphery. Peripheral vascular resistance decreases both after acute intravenous or chronic oral administration of labetalol. This is due to the agent's alpha-blocking properties. Heart rate generally falls slightly or does not change during chronic treatment.[9]

Labetalol is well absorbed from the gastrointestinal tract. Food delays the absorption of labetalol but increases its bioavailability. It undergoes extensive first-pass hepatic metabolism to an inactive glucuronide metabolite, which is excreted by the kidney. Impaired renal function does not appear to alter the half-life of the drug.

Labetalol shares the antianginal properties of the other beta blockers currently available.[10] It may be particularly useful for hypertensive patients with angina pectoris and minimal myocardial pump dysfunction. It should probably be avoided in any patient whose ventricular function is significantly impaired. Orthostatic hypotension may develop during treatment (because of its alpha-blocking properties) when larger doses of the drug are employed. Headaches and flushing (due to its vasodilating properties) may occur. Other side effects noted during labetalol treatment are similar to those of propranolol. Treatment is generally initiated at 100–200 mg, 2 or 3 times daily. At dosages exceeding 1200 mg daily, the incidence of side effects is relatively high. It will probably be marketed in 100- and 200-mg tablets.

Other adrenergic inhibiting agents

Guanabenz (Wytensin)

This is a centrally acting alpha$_2$ receptor agonist similar to clonidine and methyldopa in its antihypertensive mode of action. These agents decrease sympathetic outflow from the central nervous system to the periphery due to their stimulation of presynaptic inhibitory alpha$_2$ receptors. It is as effective as clonidine or methyldopa in the treatment of mild-to-moderate hypertension and may be used in combination with diuretics and other antihypertensive agents.[11]

Guanabenz is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations being achieved within four hours. It is extensively metabolized, and 80% of an oral dose is excreted as metabolites in the urine over a 24-hour period.

The side effects of guanabenz do not differ significantly from those of clonidine or methyldopa, but sodium retention is said to occur less commonly. Rebound hypertension may occur after the abrupt withdrawal of this agent, just as it does after the abrupt withdrawal of clonidine. It is available in 4- and 8-mg tablets and may be given twice daily in dosages of up to 64 mg/day. Dry mouth and sedation are the most common side effects.

Guanadrel (Hylorel)

Guanadrel sulfate is a postganglionic sympathetic inhibitor that does not enter the central nervous system. Hence, it does not produce central nervous system side effects such as sedation and dry mouth. Its antihypertensive mechanism of action is due to depletion of catecholamines in peripheral sympathetic neurons. Thus, peripheral resistance is decreased without a significant change in cardiac output. Its antihypertensive efficacy and mechanism of action are similar to those of guanethidine. It is approximately three fourths as potent as guanethidine, but is less likely to cause diarrhea, retrograde ejaculation, and postural hypotension.[12]

It is rapidly absorbed, and peak plasma levels are achieved in 1.5–2 hours. It is 20% protein-bound, and 85% of an oral dose is excreted in the urine. Its duration of action is much shorter than that of guanethidine (averaging nine hours versus seven days for guanethidine). Because of its relatively brief duration of action, it causes morning dizziness secondary to orthostatic hypotension less frequently than does guanethidine. It may be effective in patients with resistant hypertension, but with this exception, it will probably be utilized infrequently because of its side effects. It is available in 10- and 25-mg tablets. Treatment is usually begun at 10 mg/day and

adjusted weekly until the blood pressure is controlled or until intolerable side effects develop. The maximum recommended dose is 75 mg/day. Side effects will generally be reduced if the daily dose of guanadrel is divided when more than 40 mg of the drug is required.

Converting enzyme inhibitors

Captopril (Capoten)

Captopril is the only orally active converting enzyme inhibitor to have been marketed in the United States. Converting enzyme inhibitors reduce blood pressure by lowering peripheral vascular resistance. They seem to be particularly effective in patients with high plasma renin levels. Captopril is rapidly absorbed from the gastrointestinal tract, but food impairs absorption and it should be taken at least one hour before meals. It is excreted in the urine, partly as unchanged drug and partly as metabolites.[13]

Neutropenia and membranous glomerulopathy are the most feared side effects of captopril, but their incidence has been markedly decreased with reduction in dosage. Membranous glomerulopathy and agranulocytosis secondary to captopril are attributed to the presence of a sulfhydryl group in the captopril molecule. This sulfhydryl group is present in penicillamine, which also produces both membranous glomerulopathy and agranulocytosis on occasion. Acute renal failure has been noted after captopril administration in patients with bilateral renal artery disease, or stenosis in an artery to a solitary kidney. The etiology of this phenomenon is not known and may be multifactorial.

Side effects (both symptomatic and biochemical) are infrequent when smaller doses of the drug are given to patients with essential hypertension. This agent blunts the hypokalemic response to thiazide diuretics. Hypotension (particularly with the first dose), dysgeusia, and a maculopapular or urticarial skin rash are probably the most common side effects of the drug. Monotherapy with captopril is effective in some patients, but thiazide diuretics enhance the efficacy of the drug.[14]

Inhibition of angiotensin-converting enzyme is virtually complete after the administration of 25 mg of captopril. Larger doses of the drug induce a more prolonged rather than a more profound antihypertensive effect.[15] Captopril is available in 25-, 50-, and 100-mg tablets. Treatment is generally initiated with 12.5 to 25 mg given 2–3 times daily. Doses exceeding 450 mg/day should rarely be employed. Duration of action is prolonged in patients with chronic renal failure.

Enalapril maleate (MK-421)

Enalapril maleate is a long-acting nonsulfhydryl angiotensin-converting enzyme inhibitor that we have found to be effective (particularly when combined with a thiazide diuretic) in the treatment of patients with mild-to-moderate essential hypertension (Cressman et al, unpublished data). To date, agranulocytosis or membranous glomerulonephritis have not been reported with enalapril maleate. However, we observed one case of reversible renal glycosuria and azotemia secondary to this agent.[16]

The drug is approximately ten times as potent as captopril (on a milligram for milligram basis) and has a longer half-life, allowing for twice or possibly once daily dosing. It is converted to a diacid after absorption from the gastrointestinal tract. The diacid is the active form of the drug. Food does not interfere with the absorption of enalapril. Ten to twenty milligrams are generally given twice daily in conjunction with a thiazide diuretic. Side effects have been infrequent with this agent, but an occasional patient complains of orthostatic lightheadedness, cough, or fatigue.

Calcium channel blockers

The calcium entry blocking drugs interfere with the normal transmembrane flux of extracellular calcium ions, thus reducing contractile activity of the heart and promoting coronary and systemic vasodilatation. Hence, these agents are used in the management of ischemic heart disease and hypertrophic cardiomyopathy.[17] Clinical experience with nifedipine, verapamil, and diltiazem in the management of hypertension has been limited, but all of these agents reduce blood pressure by producing systemic vasodilatation. These agents have not yet been approved in the U.S.A. for the treatment of hypertension.

Nifedipine (Procardia)

Nifedipine is a potent arteriolar vasodilating agent that has little effect on venous capacitance vessels. Cardiac output generally increases due to a reflex tachycardia even though this agent and the other calcium channel blockers are negative inotropic drugs. A prompt and profound antihypertensive effect is observed when 10–20 mg doses of nifedipine are given orally or sublin-

gually. The antihypertensive effect is observed within 10 minutes after sublingual administration. Peak plasma levels are achieved within an hour of oral administration. Thus, it is an effective agent in patients with severe hypertension who have no evidence of serious target organ involvement.[18] Sublingual nifedipine is not generally available, but the agent can be obtained in capsules. This solution can be removed from the capsules with a syringe and given sublingually. Nifedipine is extensively metabolized before undergoing excretion in the kidney (75%) and gastrointestinal tract.

The side effects of calcium channel blockers in general, and nifedipine in particular, relate to their vasodilating effects. Headache, facial flushing, and tachycardia are the most frequent complaints. The latter can be controlled with a beta blocking agent. Pedal edema without weight gain has been noted in several patients, but its cause is unknown.

It is prudent to observe the patient closely, particularly the elderly patient, after the initial dose of nifedipine since orthostatic hypotension may be a problem. The agent has a relatively brief duration of action and is usually given three times daily. Nifedipine is available in 10-mg capsules that may be given alone or in combination with diuretics, beta blockers, or centrally acting sympatholytic agents. The addition of a beta blocker to nifedipine gives added antihypertensive and antianginal effects while decreasing the incidence of tachycardia.[19] A maximal dose of nifedipine has not been established.

Verapamil (Calan, Isoptin)

Verapamil produces hemodynamic effects generally similar to those of nifedipine, but tachycardia is less of a problem and its negative inotropic effect is more pronounced. It appears to be as effective as propranolol, pindolol, methyldopa, or nifedipine as an antihypertensive agent.[20] It may be used alone or in combination with a thiazide diuretic, but the safety of the combination of verapamil and a beta blocker (both of which have negative chronotropic and inotropic effects) needs further clarification. Gould et al,[21] using ambulatory blood pressure monitoring devices, found that verapamil in dosages of 120–160 mg given 3 times daily reduced blood pressure throughout a 24-hour period. It is well absorbed, but its bioavailability is 10%–20% because of extensive first-pass hepatic metabolism. The half-life of the drug is from 3 to 6 hours and may be as long as 9 hours during chronic administration. It is available in 80- and 120-mg tablets. Side effects include headache, constipation, epigastric pain, and burning in the gums. However, these are generally mild and transient.

Diltiazem (Cardizem)

There is little information about the use of diltiazem as an antihypertensive agent. It appears to have hemodynamic effects similar to those of verapamil.[20] Single oral doses of this agent were shown to reduce heart rate, systolic blood pressure, cardiac index, and systemic vascular resistance in hypertensive patients undergoing cardiac catheterization. Chronic diltiazem treatment also appears to be effective as monotherapy or in combination with a thiazide diuretic for the treatment of hypertension. Side effects are similar to those of verapamil. Diltiazem is well absorbed, and peak plasma levels are achieved in approximately three hours. It is 80% protein-bound and is excreted as metabolites in the urine (35%) and feces (60%). The drug is available in 30- and 60-mg tablets and should probably be given 3 times a day. As with verapamil, the maximal dose of this drug has not been established.

Conclusion

Antihypertensive agents have proliferated in the last decade. Their rational use will allow the clinician to construct an antihypertensive treatment regimen that is effective and well-tolerated in the vast majority of patients. Although many of the newer agents may be used alone, their efficacy is enhanced by the concomitant use of diuretics. A treatment program that begins with a thiazide diuretic and progresses through an adrenergic inhibiting drug and a vasodilator is still a logical approach to the hypertensive patient. Although these new agents have exciting pharmacologic properties, they have not replaced the older drugs such as hydrochlorothiazide, propranolol, or hydralazine in the treatment of hypertension.

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